REMARKS

Claims 1-16, 18-46, and 49-93 were pending. Claims 1, 5, 7, 9, 11, 12, 14-16, 55-60, 92 and 93 have been amended. Claims 8, 10, and 13 have been cancelled. Claim 94 has been added. Therefore, claims 1-7, 9, 11, 12, 14-16, 18-46, and 49-94 will be pending upon entry of the present amendment.

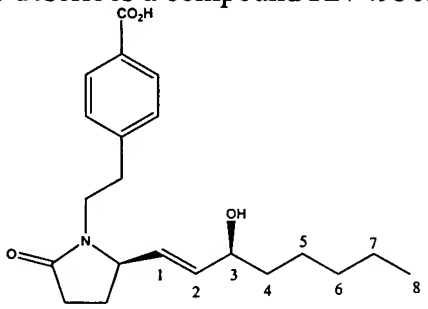
No new matter has been added. Claims 1, 5, 7, 9, 11, 12, 14-16, 55-60, 92 and 93 have been amended to clarify the invention. Support for the amendments to claims 55-59 can be found, for example, at least at page 4, lines 5-23, and page 7, lines 20-21 and 31-34 of the specification as originally filed. Claim 94 has been added. Support for claim 94 can be found, for example, at least in claim 16, as originally filed.

Applicants note with appreciation that the rejection of claim 51 under 35 U.S.C. § 112, first paragraph has been withdrawn.

Rejection of Claims 1-4, 16, 18-46, 49-55, 59, 92 and 93 under 35 U.S.C. § 102 (e)

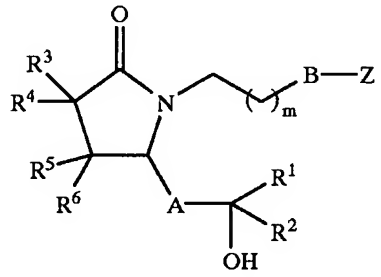
Claims 1-4, 16, 18-46, 49-55, 59, 92 and 93 are rejected under 35 U.S.C. § 102 (e) as being anticipated by Elworthy *et al.* (U.S. Patent No. 6,900,336). Applicants disagree.

Elworthy *et al.* describes a compound RN 493036-24-1 of the formula:



RN 493036-24-1

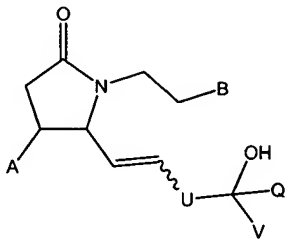
and compounds of Formula I :



Formula I

wherein R^1 is alkyl, alkenyl, alkynyl, cycloalkylalkyl, heterocyclylalkyl, aryl, arylalkyl or heteroaryl; **provided that R^1 is alkyl, alkenyl, alkynyl, cycloalkylalkyl, heterocyclylalkyl, aryl, arylalkyl or heteroaryl, when B is aryl or heteroaryl and R^3, R^4, R^5 and R^6 are not simultaneously hydrogen**, and R^1 is heterocyclylalkyl, aryl, or heteroaryl when B is absent and R^3, R^4, R^5 and R^6 are simultaneously hydrogen.

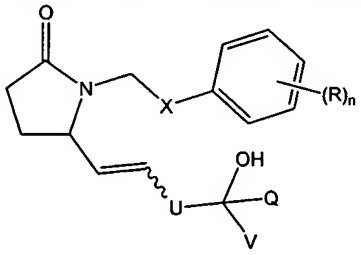
In contrast, Applicants' claims 1-4 are directed to compounds of Formula (I):



I

wherein A is hydrogen or hydroxy; B is selected from optionally substituted carbocyclic aryl and optionally substituted heteroalicyclic having from 3 to 8 ring atoms and at least 1 N, O or S ring atom or a heteroaromatic group having a single ring with 5 or 6 ring atoms and at least one N, O or S ring atom; U is $(CH_2)_p$ wherein p is selected from 0, 1 and 2; V and Q are each independently hydrogen, optionally substituted alkenyl, optionally substituted alkynyl, and $-CR^1R^2-W$, wherein R^1 and R^2 are C_1-C_6 alkyl; or R^1 and R^2 can form an C_3-C_6 cycloalkyl with the carbon they are attached to; W is selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl C_1-C_6 alkyl, aryl and heteroaryl; with at least one of V and Q being other than hydrogen. Claims 16, 18-46, 51-54, and 92 are directed to specific compounds, methods of using, and pharmaceutical compositions compounds of Formula I.

Claims 55, 59 and 93 are directed methods of using compounds of Formula II:



II

wherein R is C(=O)Z where Z is selected from hydrogen, hydroxy, optionally substituted alkoxy and optionally substituted alkyl; or R is amino or optionally substituted alkylamine; X is selected from oxygen and carbon; n is an integer selected from 0, 1, 2, 3, 4 and 5; U is $(CH_2)_p$ wherein p is selected from 0, 1 and 2; V and Q are each

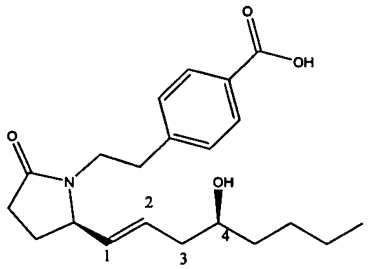
independently selected from hydrogen, optionally substituted alkenyl, optionally substituted alkynyl, and $-CR^1R^2$-W, wherein R^1 and R^2 are C_1-C_6 alkyl; or R^1 and R^2 can form an C_3-C_6 cycloalkyl with the carbon they are attached to; W is selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl C_1-C_6 alkyl, aryl and heteroaryl; with at least one of V and Q being other than hydrogen; and pharmaceutically acceptable salts thereof.

Applicants respectfully submit that Elworthy *et al.* neither teaches nor suggests compounds of Applicants' claims 1 and 55 wherein B is optionally substituted carbocyclic aryl, optionally substituted heteroalicyclic, or a heteroaromatic group, and A is hydrogen. In contrast, Elworthy *et al.* does not teach or suggest these compounds. In contrast, Elworthy *et al.* includes the proviso that when R^1 is alkyl, alkenyl, alkynyl, cycloalkylalkyl, heterocyclylalkyl, aryl, arylalkyl or heteroaryl, and B is aryl or heteroaryl, that the groups corresponding to A (R^5 and R^6) as well as R^3 and R^4 are **NOT** hydrogen.

Furthermore, Elworthy *et al.* fails to teach or suggest any compounds wherein the substituents corresponding to Applicants' A (i.e., R^5 and R^6) is hydroxy. In contrast, Elworthy *et al.* only describes compounds wherein these variables are hydrogen or C_1-C_6 alkyl.

With regard to claim 16, the Examiner alleges that "compound RN 493036-24-1 directly anticipates the first species listed." Applicants respectfully submit that this species has been deleted from claim 16, thus rendering the rejection of this claim moot.

Insofar as this rejection pertains to newly added claim 94 (which includes 4-(2-{(2*R*)-2-[(1*E*,4*S*)-4-hydroxyoct-1-enyl]-5-oxopyrrolidin-1-yl}ethyl)benzoic acid, the previously listed first species of claim 16), Applicants disagree that this species is anticipated by RN 493036-24-1. The structure of 4-(2-{(2*R*)-2-[(1*E*,4*S*)-4-hydroxyoct-1-enyl]-5-oxopyrrolidin-1-yl}ethyl)benzoic acid is:



This claimed species has a hydroxyl group at the 4-position of the alkenyl chain. In contrast, RN 493036-24-1 of Elworthy *et al.*, has a hydroxyl group at the 3-position of

the alkenyl chain. Therefore, Applicants respectfully submit that Elworthy *et al.* does not anticipate claim 94.

Therefore, Applicants respectfully request that this rejection of claims 1-4, 16, 18-46, 49-55, 59, 92 and 93 under 35 U.S.C. § 102 (e) be reconsidered and withdrawn.

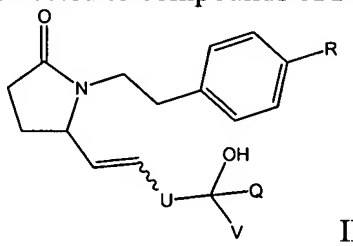
Rejection of Claims 5-12, 14-16, and 60-91 under 35 U.S.C. § 103 (a)

Claims 5-12, 14-16, and 60-91 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Elworthy *et al.* (U.S. Patent No. 6,900,336). Applicants respectfully disagree. Furthermore, claims 8 and 10 have been cancelled, thus rendering the rejection of these claims moot.

Elworthy *et al.* has been described above.

Applicants' claims 5, 6, 11, 12, 14, 15, 61-89, 90 and 91 are directed to compounds, pharmaceutical compositions and methods of using compounds of Formula II, as described above.

Applicants' claim 7 is directed to compounds of Formula III:

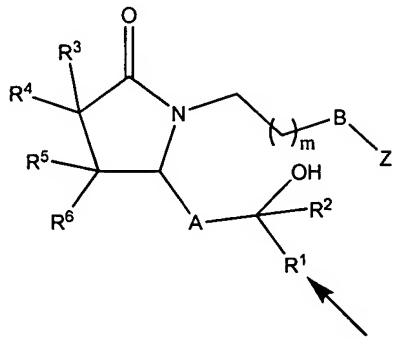


III

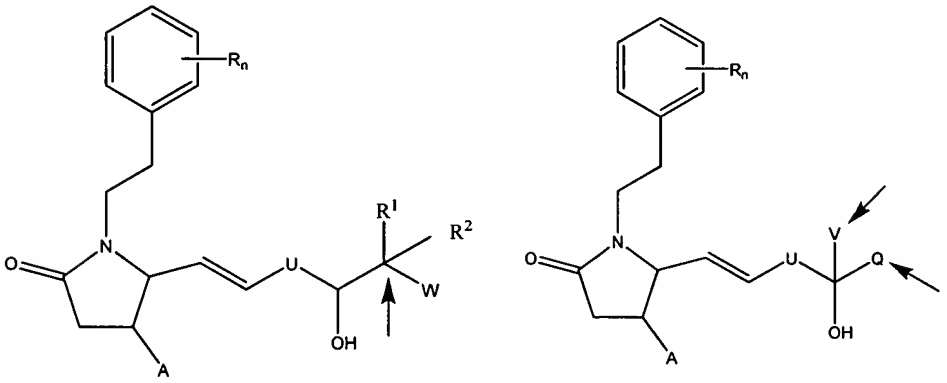
wherein R is C(=O)Z where Z is selected from hydrogen, hydroxy, optionally substituted alkoxy and optionally substituted alkyl; or R is amino or optionally substituted alkylamine; U is $(CH_2)_p$ wherein p is selected from 0, 1 and 2; V and Q are each independently selected from hydrogen, optionally substituted alkenyl, optionally substituted alkynyl, and $-CR^1R^2-W$, wherein R^1 and R^2 are C_1-C_6 alkyl; or R^1 and R^2 can form an C_3-C_6 cycloalkyl with the carbon they are attached to; W is selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl C_1-C_6 alkyl, aryl and heteroaryl; with at least one of V and Q being other than hydrogen. Applicants' claims 60-91 are directed to specific compounds, methods of using, and pharmaceutical compositions comprising compounds of Formula II.

Elworthy *et al.* fails to teach or suggest compounds wherein the group following the hydroxyl-bearing carbon atom (denoted with an arrow below) in the alkenyl side chain of the pyrrolidine core is alkenyl, alkynyl, or geminally disubstituted when B is

optionally substituted carbocyclic aryl, optionally substituted heteroalicyclic, or a heteroaromatic group, and A is hydrogen.



Formula I; Elworthy *et al.*



Applicants' Compounds

In addition, the compounds of Applicants' claims 5, 7, 16, and 60 have outstanding, selective agonist properties when compared to those described in Elworthy *et al.* This exceptional pharmaceutical activity includes advantageous binding selectivity to the EP4 receptor, as disclosed in the instant specification page 7, lines 20-21. The surprising activity is further shown in Table 1 on pages 106-107. In particular, the Examiner should note the activity of the geminally disubstituted compound 5. Applicants note that compound 5 binds strongly to the EP4 receptor with a K_i value of 0.73 nM, while binding weakly to the EP2 receptor with a K_i value of 1237 nM. These data illustrate compound 5's excellent selectivity towards the EP4 receptor.

In contrast, Elworthy *et al.* describes compound RN 493036-24-1. This compound corresponds to Applicants' compound 1 as described in Table 1 on pages 106-107 of the specification. Compound 1 binds to the EP4 receptor with a K_i value of 120 and an EC_{50} of 15 nM. In addition, compound 1 binds to the EP2 receptor with a K_i value of 2 and an EC_{50} value of 0.002 nM. Thus, compound 1 has a less pronounced

selectivity for the EP4 receptor over the EP2 receptor and a weaker binding activity towards the EP4 receptor as compared to Applicants' compound 5.

One of ordinary skill in the art would not have been motivated to prepare the geminally disubstituted claimed compounds, because the resulting exceptional selectivity is both surprising and unexpected. Elworthy *et al.* neither teaches nor suggests such geminal di-substitution.

Therefore, Applicants respectfully submit that Elworthy *et al.* does not render claims 5-12, 14-16, and 60-91 obvious, and request that this rejection under U.S.C. § 103(a) be withdrawn.

Objections to the Claims

Claims 13, 16, 55, 56-58, and 60 are objected to by the Examiner. Claim 13 has been cancelled, thus rendering the objection to this claim moot.

Claim 16 was objected to, in part, as not including every limitation of claim 1, the claim from which claim 16 depends, because some of the species therein include branched alkyl groups. Applicants respectfully submit that this rejection no longer pertains to claim 16 as currently amended.

The Examiner has objected to claims 16 and 60 because of the failure to include "and" between the last two species of each claim. Applicants respectfully submit that this objection no longer applies to claims 16 and 60 as currently amended and request that this objection be withdrawn.

Claim 55 was objected to by the Examiner because the Examiner alleges that the drawing of Formula (VI) is unclear. Applicants respectfully submit that this objection no longer pertains to claim 55 as currently amended and request the withdrawal of the objection.

With respect to claims 56-58, Applicants note with appreciation that claims 56-58 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants respectfully submit that the objection of the base claim should be withdrawn for the aforementioned reasons, thus rendering claims 56-58 allowable.

Therefore, Applicants respectfully request that the objections to claims 13, 16, 55, 56-58, and 60 be withdrawn.

SUMMARY

Amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections. The amendments to and/or cancellation of the claims are being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application. The amendments made to the claims are not related to any issues of patentability.

In view of the foregoing, entry of the amendments and remarks presented herein, favorable reconsideration and withdrawal of the rejections, and allowance of this application with all pending claims are respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is invited to call the undersigned at (617) 227-7400.

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